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TITLE: Timing of Surgery and Rehabilitation to Optimize Outcome for Patients with Multiple Ligament Knee Injuries: A Multicenter Clinical Trial

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| 14. ABSTRACT Multiple ligament knee injuries (MLKIs) are complex injuries that represent a spectrum of injury ranging from disruption of two ligaments (one cruciate ligament and one collateral ligament) to all four ligaments (both cruciates and both collateral ligaments). Multiple ligament knee injuries are frequently associated with concomitant injuries to nerves, vessels, tendons, cartilage and menisci. Non-operative management of MLKIs results in poor outcomes; however there is no consensus on the optimal surgical approach for MLKIs. Level III evidence suggests that in comparison to delayed surgery, early surgical management of MLKIs leads to better clinical outcomes, but is associated with a higher risk of loss of motion and joint contracture. Suboptimal outcomes for treatment of MLKIs include persistent pain, stiffness, residual instability and laxity, loss of motion and limited ability to perform demanding activities associated with military training, heavy physical labor and sports. | | | | | |
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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The overall purpose of this Clinical Trial Development Award (CTDA) is to plan a multicenter randomized clinical trial to investigate the effects of timing of surgery and rehabilitation to optimize clinical outcome and return to duty/activity for military personnel and civilians with a multiple ligament knee injury (MLKI). We hypothesize that early surgery and early initiation of post-operative rehabilitation will lead to improved outcomes in terms of: 1) return to duty/work and sports, 2) patient-reported and performance-based measures of physical function and health-related quality of life; 3) restoration of normal laxity and range of motion with 4) no increased risk of complications. The overarching objectives for the CTDA are to: 1) further develop the research network to ensure access to a population of individuals with a MLKI injury that is necessary for successful recruitment of the required number of subjects; 2) finalize the experimental design including issues related to subject eligibility, randomization and outcome measurement; 3) develop clinical protocols for surgery and post-operative rehabilitation; 4) finalize the required sample size and develop the statistical analysis and data management plans; 5) develop a clinical and safety monitoring plan; 6) establish a governance structure to oversee conduct of the study; 7) develop a site monitoring plan that includes guidelines for closing and adding sites; and 8) develop a transition plan to move to implementation of the clinical trial.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Multiple ligament knee injury; timing of surgery; timing of post-operative rehabilitation; optimizing return to activity/duty; patient-reported outcome.

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

Under the approved SOW, the project had the following major goals:

- 1) Develop Research Network for Multicenter Clinical Trial
- 2) Finalize Experimental Design
- 3) Develop Clinical Protocols
- 4) Finalize Sample Size and Develop Statistical Analysis & Data Management Plan
- 5) Establish Governance Structure to Oversee Study Management
- 6) Develop Clinical and Safety Monitoring Plan
- 7) Develop Site Monitoring Plan
- 8) Develop Transition Plan to Move to Clinical Trial
- 9) Prepare and Submit Application for Clinical Trial Award to Conduct Trial

What was accomplished under these goals?

1) Develop Research Network for Multicenter Clinical Trial (Task 1)

- a) During this project period 2 additional clinical sites (University of Cincinnati and University of Washington) were added to the research network, bringing the total number of clinical sites for this study to 24. The research network includes 5 US military treatment centers and 3 Canadian and 16 US civilian centers for excellence for the treatment of complex knee injuries. Investigators at all sites continued to express interest and commitment to participating in the multicenter clinical trial and have participated in the regular investigator conference calls and two in-person investigators' meetings.
- b) A medical record review to determine the mechanism of injury, timing of presentation and injury pattern of multiple ligament knee injuries (MLKIs) as well as associated injuries was completed. IRB approvals for chart review activities were obtained from 16 sites and chart review data was provided from 13 sites. In total 999 individuals with a MLKI were reviewed. The results were included as preliminary data in the grant application for an Integrated Clinical Trial Award to support the conduct of the study. Additionally, an abstract summarizing the results of this retrospective study was submitted and accepted for presentation at the 2018 Annual Meeting of the American Orthopaedic Society for Sports Medicine.
- c) Conference calls with investigators from the collaborating clinical sites have been held on a regular basis. During these calls the investigators discussed issues related to the design of the clinical trial (subject eligibility criteria, study interventions, primary and secondary outcomes, etc.), budget and overall governance structure for the multicenter clinical trial.
- d) Two Investigators' Meeting were held during this project period. The first was March 14, 2017 at the AAOS Annual Meeting in San Diego; the second was July 21, 2017 at the AOSSM Annual Meeting in Toronto, ON. The meetings covered the topics related to the timeline for submission and review of the grant application, summary and review of the results of the retrospective review study, overview of IRB and HRPO regulatory procedures, coordinating site responsibilities, clinical site responsibilities and budget.
- e) An in-person meeting of the Rehabilitation Committee was held on August 25, 2017 in Pittsburgh. At this meeting the rehabilitation protocol for the early and delayed post-operative rehabilitation programs were reviewed and finalized. Additionally, case report forms related to assessment of adherence to the post-operative rehabilitation as randomized and materials for communications to subjects and rehabilitation providers were reviewed and approved. Lastly, the development of training modules to educate the physical therapists providing the post-operative rehabilitation were planned and discussed.

2) Finalize Experimental Design and Develop Clinical Protocols (Task 2 and Task 3)

- a) The study specific aims were revised and approved by the study investigators. They include:

Specific Aim 1: Determine the effects of timing of surgery and post-operative rehabilitation on time to return to pre-injury level of military duty, work and sports and patient-reported physical function. It was hypothesized that early surgery, early rehabilitation and the combination or early surgery with early rehabilitation will lead to an earlier and more complete return to pre-injury military duty, work and sports activity and better patient reported physical function.

Specific Aim 2: Determine the effects of timing of rehabilitation on time to return pre-injury level of military duty, work and sports and patient-reported physical function. It was hypothesized that early rehabilitation will lead to an earlier and more complete return to pre-injury military duty, work and sports activity and better patient-reported physical function.

Due to budget constraints for the Integrated Clinical Trial Award, plans to enroll individuals that had a MLKI that precluded randomization to surgery or rehabilitation into a parallel observations study were eliminated from the project.

b) Investigators finalized the eligibility criteria for each of the study objectives. The final eligibility criteria were:

Male and female military personnel and civilians between the ages of 16 and 55 with a MLKI (defined as a complete grade III injury of two or more ligaments) without a history of prior knee ligament reconstruction with or without a nerve injury or tendon rupture or avulsion will be eligible to participate in the proposed integrated clinical trials. Individuals with a torn or avulsed patellar or quadriceps tendon, periarticular fracture that requires surgical reduction and fixation (i.e. KD V injury classification) or use of an external fixator to maintain reduction of the knee for greater than 10 days, that are unable to WB on the contralateral uninjured leg, or have a traumatic brain injury (TBI) that limits their ability to participate in their post-operative care will be excluded from participation in these studies.

To be eligible to participate in the study for Specific Aim 1 individuals with a MLKI must present to orthopaedic surgery in time to undergo definitive surgery within 6 weeks if randomized to the early surgery group. Individuals with a vascular injury that dictates the timing of surgery, polytrauma that precludes surgery within 6 weeks, or a skin or soft tissue injury that precludes randomization to early surgery or early rehabilitation will be excluded from the study for Specific Aim 1. Individuals will also be excluded from participation in the study for Specific Aim 1 if they can not be randomized to early rehabilitation because the surgical procedure precludes early post-op WB and ROM (i.e. surgery for extensor mechanism rupture or avulsion, vascular graft surgery).

Subjects with a MLKI that present to orthopaedic surgery at a time the precludes randomization to early surgery or have an injury that precludes randomizing the timing of surgery (such as a vascular injury) as well as those that refuse randomization to the timing of surgery will be eligible to participate in the study for Specific Aim 2, in which subjects are randomized to only early vs. delayed rehabilitation. Individuals that can not be randomized to early rehabilitation including those that are unable to WB on the opposite limb, or have a skin or soft tissue injury or undergo a surgical procedure that precludes early weightbearing and ROM (i.e. surgery for extensor mechanism rupture or avulsion, vascular graft surgery) will also be excluded from participation in this study for Specific Aim 2.

c) The primary and secondary outcomes of the clinical trial were finalized by the investigators.

The primary outcome will be time to return to full pre-injury military duty, work and sports. Patient-reported physical function as measured with the Activities Limitation Scale of the Multiple Ligament Quality of Life (MLQoL) Questionnaire will be assessed as a secondary primary outcome 6, 12 and 24 months after randomization. To more precisely measure the time to return to pre-injury military duty, work and sports, a brief Return to Activity Monitoring Survey will be administered on a monthly basis starting 6 months after randomization and continuing through the 24-month follow-up. To determine successful return to activity will compare patient-reported measures of military duty, work and sports to the individual's pre-injury level of military duty, work and sports. Individuals will be classified as having returned to activity if and when they have returned to their pre-injury level of military duty, work and sports.

Secondary outcome measures will include additional knee-specific and general patient-reported measures of physical function and health related quality of life, recovery of range of motion (ROM), arthrofibrosis, residual laxity, complications/adverse events, re-injury and additional surgical procedures.

d) The Executive Committee in conjunction with the study investigators have developed and agreed upon the definitions for early surgery (repair and/or reconstruction within 6 weeks of injury) and delayed surgery (repair and/or reconstruction 12 to 16 weeks after injury).

e) The Rehabilitation Committee in conjunction with the study investigators have developed and agreed upon the early and delayed post-operative rehabilitation guidelines, as well as the universal rehabilitation procedures that will apply to all subjects regardless of group assignment.

3) Finalize Sample Size and Develop Statistical Analysis & Data Management Plan (Task 4)

a) The sample size and statistical analysis and data management plans for the multicenter clinical trial was finalized. As described below, the sample size analyses indicated that 392 subjects are necessary for the trial that randomizes the timing of surgery and rehabilitation and 298 are subjects are needed

Based on our preliminary retrospective study, we estimated that across 23 clinical sites there will be 1213 MLKIs over a 2-year recruitment period. After the exclusions for participation in the trial that randomizes timing of surgery and rehabilitation (*Aim 1*), we estimated that there will be approximately 650 eligible individuals with a MLKI that present to orthopaedics in time to make it possible to perform surgery within 6 weeks if randomized to early surgery. Assuming that approximately 60% of the eligible subjects agree to participate in the study, this would provide a total sample size of 392 (n= 98 per cell). Assuming 10% lost to follow-up over two years, we expect to have 352 subjects (n=88 per cell). This sample size would provide 80%-92% power to detect a 15% absolute difference ($\alpha=0.05$) at 24 months follow-up in the rate of return to full pre-injury military duty, work and sports for the main effects (n=176 for each arm) for timing of surgery or timing of rehabilitation, assuming the delayed arm has a return rate of 30% to 70%. Additionally, we would have 80% power to detect a 17% to 21% absolute difference between the early surgery/early rehabilitation group (n=88) compared to any of the other 3 groups with rates from 30%-70%. With 176 subjects per main effect arm, we would have 82% power to detect a

15% difference in return to military duty, work and sports (hazard ratio=0.65, 35% improvement in the time to rate of return to duty, work and sports) using a log-rank test assuming two-year accrual, two-year follow-up for each participant, 10% dropout in each arm, and 5% crossover in each arm.

For the MLQoL Questionnaire Activity Limitations Scale, we determined that we would have 80% power to detect a 6.2 point difference at 24 months between early surgery and delayed surgery (or early rehabilitation and delayed rehabilitation) using a two-sided two-sample equal variance t-test ($\alpha=0.05$, standard deviation=20.8) assuming a 10% attrition rate. This is equivalent to a small effect size of approximately 0.30. We would also have 80% power to detect a 10.2-point difference between the early surgery/early rehabilitation group and any of the other three groups using the same standard deviation and test ($\alpha=0.0167$ adjustment for multiple comparisons).

For the trial in which subjects are only randomized to early vs. delayed rehabilitation (Aim 2), a total of 298 subjects randomized, would provide 79% to 84% power to detect an absolute difference of 15% between the groups assuming the delayed rehabilitation group has a return to military duty, work and sports rate of 65 to 70% and 10% attrition.

b) The data analysis plan for Aims 1 and 2 was finalized. All analyses will follow the principle of intention-to-treat principle. The primary outcome of return to military duty, work and sports will be assessed at monthly intervals via text message, email, or phone call from 6 to 24 months after randomization. This frequency of measurement will allow us to conduct more precise time to event analysis compared to having discrete time points several months apart. For those participants not returning to full activity and participation, the date of censoring for each participant will be the end of the two year follow up or last contact prior to 4 consecutive months of non-response/no data for this outcome.

For the trial in which subjects are randomized to timing of surgery and timing of post-operative rehabilitation (Aim 1), we will estimate and compare the time to event curves using Kaplan-Meier estimation and log-rank tests. Although we are not powered for detecting an interaction, we will test the interaction between timing of surgery and timing of rehabilitation using a Cox proportional hazards model prior to looking at main effects. Assuming the interaction is not significant, we will compare the time to return to return to military duty, work and sports for both main effects, adjusting for site and the knee dislocation injury pattern. We will present results using hazard ratios and 95% confidence intervals.

Linear mixed models will be used to compare and test the mean patient-reported physical function across the groups accounting for repeated measurements within patient. The fixed effects of surgery (early vs. delayed), rehabilitation (early vs. delayed), time (baseline, 6, 12, 24 months), the two-way interactions, and the three-way interaction will be placed in the model controlling for site and KD injury pattern. Assuming the 3-way interaction is not significant, we will proceed to test the two-way interactions for surgery*time and rehabilitation*time. If the two-way interaction is significant, we will test the separate treatment effects at 24 months (primary time point of interest) using contrasts. All treatment effects will be presented using adjusted mean differences and 95% confidence intervals.

To determine if early surgery and early rehabilitation is better than the other combinations, we will specifically compare the early surgery/early rehabilitation group to each of the 3 other intervention arms using contrasts in the full models for both the time to event outcome and patient-reported physical function.

We will use similar statistical procedures for analysis of the trial that randomizes only timing of rehabilitation (Aim 2). Time to full return to activity and participation will be estimated using Kaplan Meier curves and log-rank tests will be used to determine differences between the two groups. We will then test the curves adjusting for site and knee dislocation injury pattern using Cox proportional hazards model similar to the analysis in Aim 1. We will use linear mixed models to compare and test the mean patient-reported physical function between the two groups over time accounting for the repeated measurements within patient. The fixed effects of early vs. delayed rehabilitation and time (baseline, 6, 12, and 24 months) and their two-way interaction will be tested adjusting for site and knee dislocation injury pattern.

c) An electronic data management system has been developed by the Data Center at the University of Pittsburgh using the REDCap data capture system. Data collection forms have been built for screening, contact information, demographic and participant information, baseline clinical examination, inclusion/exclusion criteria, patient reported outcomes, surgical findings and procedures, clinic follow-up visit, rehabilitation adherence and assessment of return to activity. Additionally, event driven forms related to adverse events/serious adverse events, change in participant status and protocol deviations have been developed and converted to electronic format in REDCap. The baseline clinical examination and surgical forms underwent pilot testing and the results were used to revise and streamline the forms.

4) Establish Governance Structure to Oversee Study Management (Task 5)

a) The overall governance structure for the clinical trial has been established. This includes the establishment of the Executive Steering Committee as well as the Forms, Publications & Ancillary Studies, Quality Control, Recruitment and Adverse Event Committees.

b) The Executive Steering Committee consists of 10 members representing military and civilian sites, as well as geographic location. Members of the committee are James Irrgang (Chair), Volker Musahl (Co-Chair), Travis Burns, Christopher Harner, Bruce Levy, Andrew Lynch, Charity Moore, Brett Owens, Robert Schenck, Daniel Whelan. The Executive Steering Committee provides oversight and direction for the trial. The Committee will define the vision and the scientific goals of the STaR Trial, review and approve the final study protocol and any proposed future modifications, monitor study progress including recruitment, retention, and site compliance with study procedures, resolve any conflicts that arise between investigators and review and issue final approval or recommend modification for all subcommittee decisions. The Executive Steering Committee has met monthly or more frequently over the last year.

b) The Executive Steering Committee established and defined the purpose, structure and function of the Forms, Publications & Ancillary Studies, Rehabilitation, Quality Control, Recruitment, and Adverse Events Adjudication Committees.

- The Forms Committee has drafted a set of forms for use in the proposed trial. Going forward, the Forms Committee will review and approve all form modifications, will regularly review and maintain a current set of approved forms and maintain a log of all form changes throughout the duration of the trial.
- The Publications and Ancillary Studies Committee has established the policies and procedures for assigning working groups and approving STaR Trial-associated ancillary studies, secondary analyses of existing data and abstracts, presentations, and publications prior to their submission for dissemination. This Committee has also established guidelines for authorship for investigators following the guidelines specified by the International Committee of Medical Journal Editors. The Publications and Ancillary Studies Committee reviewed and approved a manuscript summarizing the post-operative rehabilitation program that was published in *Current Reviews in Musculoskeletal Medicine* and an abstract summarizing the multicenter retrospective review study of MLKIs that was submitted and accepted for presentation at the 2018 Annual Meeting of the American Academy of Orthopaedic Surgery.
- The Rehabilitation Committee has established the guidelines and protocols for early and delayed post-operative rehabilitation protocols that will be investigated in this study. Additionally, the Committee will ensure training and standardization of the rehabilitation procedures at all study sites through the development of training materials and learning modules. The Committee also created materials for home exercise programs and will create procedures to monitor and maximize compliance with rehabilitation procedures at all sites. Currently the Rehabilitation Committee is considering an online vendor to provide training for the physical therapists that will provide the post-operative rehabilitation and to provide the study participants with access to an online home exercise program.
- A Quality Control Committee will be established to review and affirm the quality of the conduct of the trial including implementation of the surgical and rehabilitation interventions as randomized. The Quality Control Committee will oversee implementation of the study protocol, monitor the study data for completion of study procedures and for missing data, review loss to follow-up and protocol deviations in aggregate as well as by site and will be responsible for the oversight of site monitoring visits.
- A Recruitment Committee will be established to create recruitment materials and to monitor recruitment and follow-up throughout the duration of the trial. Additionally, should a site be recruiting fewer subjects than recommended, the committee will evaluate the site and make recommendations to improve recruitment or termination of the site.
- The Adverse Events Adjudication Committee will include three individuals external to the study investigators and will be responsible for reviewing and adjudicating any and all adverse events. The composition of the Adverse Events Adjudication Committee will be established prior to beginning the full clinical trial.

5) Develop Clinical and Safety Monitoring Plan (Task 6)

a) A Clinical Monitoring Plan has been established to create guidelines for and conduct of site monitoring visits and related tasks for monitoring the STaR Trial. As the Clinical Coordinating Center, the University of Pittsburgh will be responsible for Clinical Monitoring Plan under the leadership of Dr. Alexandra Gil, Co-Investigator and Quality Control Coordinator, and Maria Beatrice Catelani, Project Coordinator, in collaboration with Drs. Irrgang (Principal Investigator), Musahl (Co-Principal Investigator and Qualified Clinical Investigator for Surgery)

and Lynch (Co-Investigator and Qualified Clinical Investigator for Rehabilitation) as well as Dr. Charity Moore, (Co-Investigator and Director of the Data Coordinating Center). Dr. Gil and Ms. Catelani will serve as the Clinical Trial Monitors. The intent of the Clinical Monitoring Plan is to ensure compliance with the research protocol, the International Conference on Harmonization (ICH) Good Clinical Practice Guidelines, national and local regulations, and institutional policies across all sites. The focus of the Clinical Monitoring Plan includes: 1) site assessment review and staff training; 2) human subjects' protection; 3) protocol compliance; 4) regulatory compliance; 5) quality assurance; 6) adverse event reporting; and 7) integrity of research data. Implementation of the Clinical Monitoring Plan will include continuous year round remote monitoring, such as review of electronic records and regular communication with Research Coordinators (e.g. biweekly phone calls) and annual on-site monitoring visits.

b) A Data and Safety Monitoring Plan (DSMP) has been developed to oversee the conduct of the study to ensure the integrity of the data and safety and protection of subjects. An independent Data and Safety Monitoring Board (DSMB) will be convened to implement the DSMP. Logistical support for the DSMB will be provided by the University of Pittsburgh Clinical and Translational Science Institute. The DSMB will consist of 7 individuals who have no financial, scientific, or other conflicts of interest with the trial and will include 3 orthopaedic surgeons and 3 physical therapists, one each representing military, Canadian and US civilian interests and a biostatistician. Prior to the start of recruitment, the DSMB will review the research protocol, informed consent documents and plans for data and safety monitoring and will issue approval for the start of enrollment into the study. After enrollment begins, the DSMB will meet every 6 months to evaluate progress of the trial, consider factors external to the study, review clinical center performance, protect and report on safety of the subjects, monitor confidentiality of the trial and make recommendations concerning continuation, termination or other modifications of the trial. Templates for open and closed reports for the DSMB have been developed.

c) During this funding period, we have designated the trial to be greater than minimal risk. As such it has been determined that a Research Monitor will be necessary. Duties of the Research Monitor will include oversight of study interactions or interventions, data collection, data storage and analysis, and review of monitoring plans and unanticipated problems involving risk to participants or others. The Research Monitor will consult on individual cases as necessary and will review and evaluate adverse event reports. The Research Monitor may discuss the research protocol with the investigators, interview subjects, consult with others outside of the study about the research and will promptly report any discrepancies or problems to the IRB. Site-specific Research Monitors may also be appointed to observe local subject recruitment, enrollment and/or the consent process. The Research Monitor will have the authority to stop the research study in progress, remove individuals from a study, and/or take any steps to protect the safety and well-being of subjects until the IRB can make an assessment.

6) Develop Site Monitoring Plan (Task 7)

a) The Clinical Monitoring Plan that was described above will include four types monitoring visits including a Site Initiation Visit, Interim Visits, For-Cause Visits and Study Close-Out Visit. The Site Initiation Visit will occur prior to site activation once IRB and Human Research Protections Office (HRPO) approvals and all subcontracts and agreements are in place. During

the Site Initiation Visit preparedness of the site to execute the research protocol will be confirmed and any necessary training will be provided.

The first Interim Visit will be conducted remotely for each site after 2 to 3 subjects have been enrolled and followed for 3 to 6 months. Subsequent Interim Visits will be onsite and conducted annually. Subsequent onsite Interim Visits will be conducted annually. These visits will ensure that the subjects' rights are being protected, the study is being conducted according to the protocol and application regulations and that the interventions, subject safety data and study endpoints are being accurately reported.

For-Cause Visits will be conducted to address any unanticipated issues that arise which require training, remediation or other situations for which the site requires assistance. For-Cause Visits will be conducted remotely or on-site if mandated by the Quality Control Coordinator, PI, or Director of the Data Coordinating Center.

The Close-Out Visit will be conducted to ensure that all study data and other study documentation is complete and accurate and that all study records have been reconciled. Close-Out Visits will be conducted at the completion of the study or earlier in the case of termination of the site's participation in the study or termination of the study overall.

7) Develop Transition Plan to Move to Clinical Trial (Task 8)

a) Data collection forms have been developed for recording clinical findings, surgical findings and procedures, patient reported outcome measures, adverse events, complications, and subject tracking. Approximately 90% of these forms have been converted to electronic format for a web-based electronic data capture system using REDCap. Testing and debugging the electronic data capture system will be completed in January 2018 under the no cost extension that has been approved.

b) A Clinical Protocol, Manual of Operations and related training materials are under development and will be completed by February 2018 under the no cost extension that has been approved and will be distributed prior to the beginning of the clinical trial.

c) The University of Pittsburgh Institutional Review Board (IRB) will serve as the single IRB of record for all US military and civilian sites. The SMARTIRB process will be used to facilitate the execution of the reliance agreements with the US civilian sites. Separate reliance agreements will be established with the US military sites. The University of Pittsburgh IRB can not serve as the IRB of record for the Canadian sites and as such, each Canadian site will need to obtain local IRB approval for the study. It is expected that IRB approval at the University of Pittsburgh will be obtained by the end of November 2017. At that time, the protocol and consent forms will be submitted to the Department of Defense for review and approval by the Human Research Protections Office (HRPO). Following HRPO approval, any necessary modifications in the protocol or consent forms will be submitted to the University of Pittsburgh IRB. Once perfected, the IRB protocol and consent forms will be submitted to all of the sites for their review, consideration and adoption.

8) Prepare and Submit Application for CTA to Conduct Trial (Task 9)

a) The full application for the Integrated Clinical Trial Award (Funding Opportunity: W81XWH-16-PRORP-ICTA) was submitted on December 6, 2017. The investigators received notice that the DoD intended to fund the project on May 30, 2017, pending appropriate responses to the scientific and administrative review. The final notice of the award, indicating approval of the project was received September 30, 2017.

What opportunities for training and professional development has the project provided?

On February 16, 2017, members of the Rehabilitation Committee presented the guidelines and protocols for post-operative rehabilitation of a multiple ligament knee injury during an educational session at the Combined Sections Meeting of the American Physical Therapy Association.

A manuscript summarizing the post-operative rehabilitation guidelines following surgery for a MLKI was published in Current Reviews in Musculoskeletal Medicine. A copy of the published manuscript with is attached to this Annual Report The complete reference is:

Lynch AD, Chmielewski T, Baily L, Stuart M, Cooper J, Coady, C, Sgroi T, Owens J, Schenck R, Whelan D, Musahl V, Irrgang J, STaR Trial Investigators: Current concepts and controversies in rehabilitation after multiple ligament knee surgery. Current Reviews in Musculoskeletal Medicine, DOI 10.1007/s12178-017-9425-4, published online Aug 4, 2017.

An abstract summarizing the retrospective review of multiple ligament knee injuries was submitted and accepted for presentation at the Annual Meeting of the American Academy of Orthopaedic Surgery on March 9, 2017. A copy of the submitted abstract is attached to this annual report. The reference for the abstract is:

Irrgang JJ, Lynch AD, Burns TC, Harner CD, Levy BA, Owens, BD, Schenck RC, Musahl V, Oostdyk, A, Popchak A, Burnham JM, Moore-Patterson C, Getgood A, Hodax J, Cooper JM, Ranawat AS, Marx RG, Coady CM, Wong IHB, Macalena JA, Nelson BJ, Arciero RA, Edgar C, Cote M, Johnson DL, Jacob C, Richter D, Treme G, Vietch AJ, Wascher DC, Black BS, Bailey L, Miller MD, Hart J: Mechanism, presentation, injury pattern and associated injuries for multiple ligament knee injuries: A multicenter study from the surgical timing and rehabilitation (STaR) trial for MLKIs Network. Presented at the Annual Meeting of the American Academy of Orthopaedic Surgeons, New Orleans, LA, March 9, 2017.

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

A no cost extension request was submitted for this project to complete the planning activities for the clinical trial. These activities include completion and testing of the electronic data capture system for the study, translation of patient-facing study materials (recruitment flyers, screening and verbal consent forms, informed consent forms and all patient-reported measures) into Spanish and completion of the clinical protocol and manual of operations.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report.

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals.

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Lynch AD, Chmielewski T, Baily L, Stuart M, Cooper J, Coady, C, Sgroi T, Owens J, Schenck R, Whelan D, Musahl V, Irrgang J, STaR Trial Investigators: Current concepts and controversies in rehabilitation after multiple ligament knee surgery. Current Reviews in Musculoskeletal Medicine, DOI 10.1007/s12178-017-9425-4, published online Aug 4, 2017.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers, and presentations.

Lynch AD, Bailey L; Burns T; Owens J; Irrgang JJ: Managing the Chaos: Rehabilitation of Multiple Ligament Knee Injuries. Accepted for presentation at the Combined Sections Meeting of the American Physical Therapy Association. San Antonio, TX, February 16, 2017

- **Website(s) or other Internet site(s)**

Nothing to Report.

- **Technologies or techniques**

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

Nothing to Report.

- **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: James Irrgang
Project Role: Principal Investigator
Nearest person month worked: 1
Contribution to Project: Dr. Irrgang has been responsible for overseeing and ensuring completion of all planning activities that were conducted during this funding period.

Name: Volker Musahl
Project Role: Co-Investigator
Nearest person month worked: 1
Contribution to Project: Dr. Musahl has been instrumental in developing and refining the subject eligibility criteria, developing the surgical protocol and developing and testing the surgical forms that will be utilized during the study. He has participated in the monthly conference calls.

Name: Charity Moore Patterson
Project Role: Co-Investigator
Nearest person month worked: 1
Contribution to Project: Dr. Moore-Patterson has been instrumental in assisting with study design, data analysis plan and sample size calculations for the full clinical trial application. In addition, she oversaw the development of the electronic data capture system at Carolinas Healthcare System.

Name: Alicia Oostdyk
Project Role: Project Coordinator
Nearest person month worked: 3
Contribution to Project: Ms. Oostdyk has participated in the monthly conference calls. She made substantial contributions to grant application and has worked with Dr. Moore-Patterson to generate the initial drafts of the case report forms.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Change in Other Support for Irrgang JJ:

Title: Predicting the Outcome of Exercise Therapy for Treatment of Rotator Cuff Tears

Time: Commitment 7.5% (0.90 calendar months)

Role: Co-Principal Investigator

Supporting Agency: National Institute of Arthritis and Musculoskeletal and Skin Diseases

Name and Address of the Funding Agency's Procuring Contracting /Grant Officer:

Gail Hamilton

Democracy I, Room: 844

hamiltog@mail.nih.gov

Performance Period: 09/01/2016 – 05/31/2021

Level of Funding: \$281,183

Brief Description of Project Goals:

The overall goal of the proposed project is to conduct a prospective observational cohort study to describe the effects of exercise therapy in terms of patient-reported and structural outcomes, as well as to identify predictors of these outcomes in patients with an isolated supraspinatus tear.

What other organizations were involved as partners?

Organization Name: Brown University

Location of Organization: Providence, RI, USA

Partner's contribution to the project: Collaboration and Other: data

Organization Name: Carolinas Healthcare

Location of Organization: Charlotte, NC, USA

Partner's contribution to the project: Collaboration

Organization Name: HealthPartners

Location of Organization: Minneapolis, MN, USA

Partner's contribution to the project: Collaboration and Other: data

Organization Name: Hospital for Special Surgery

Location of Organization: New York City, NY, USA

Partner's contribution to the project: Collaboration and Other: data

Organization Name: Mayo Clinic

Location of Organization: Rochester, MN, USA

Partner's contribution to the project: Collaboration

Organization Name: TRIA/University of Minnesota

Location of Organization: Minneapolis, MN, USA

Partner's contribution to the project: Collaboration, and Other: data

Organization Name: University of Connecticut

Location of Organization: Storrs, CT, USA

Partner's contribution to the project: Collaboration, and Other: data

Organization Name: University of Kentucky

Location of Organization: Lexington, KY, USA

Partner's contribution to the project: Collaboration, and Other: data

Organization Name: University of New Mexico

Location of Organization: Albuquerque, NM, USA

Partner's contribution to the project: Collaboration, and Other: data

Organization Name: University of Virginia

Location of Organization: Charlottesville, VA, USA

Partner's contribution to the project: Collaboration, and Other: data

Organization Name: Washington University in St. Louis

Location of Organization: St. Louis, MO, USA

Partner's contribution to the project: Collaboration

Organization Name: San Antonio Military Medical Center

Location of Organization: San Antonio, TX, USA

Partner's contribution to the project: Collaboration and Other: data

Organization Name: Western University / Fowler Kennedy Sports Medicine Clinic

Location of Organization: London, ON, Canada

Partner's contribution to the project: Collaboration, and Other: data

Organization Name: St. Michael's Hospital

Location of Organization: Toronto, ON, Canada

Partner's contribution to the project: Collaboration

Organization Name: Nova Scotia Health Authority

Location of Organization: Halifax, NS, Canada

Partner's contribution to the project: Collaboration, and Other: data

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9. APPENDICES: N/A